Receptors

General Signaling Types

Cells communicate in two general ways: electrically and chemically. An electrical charge dissipates quickly with distance, and it relies upon the special property of excitable cells to allow an electrical signal to propagate (#7: *Action Potentials*). Electrical signaling must occur over a membrane, so will either terminate with the end of the cell, or propagate via **gap junctions**, special connections that communicate **electrical signals** by physically linking the cytoplasm of two neighboring cells, as in cardiac myocytes. Many epithelial layers are connected by gap junctions.

In this lesson, we'll discuss a means of communicating a signal over a much greater distance than between two cells opposed to one another and physically connected. This is chemical signaling.

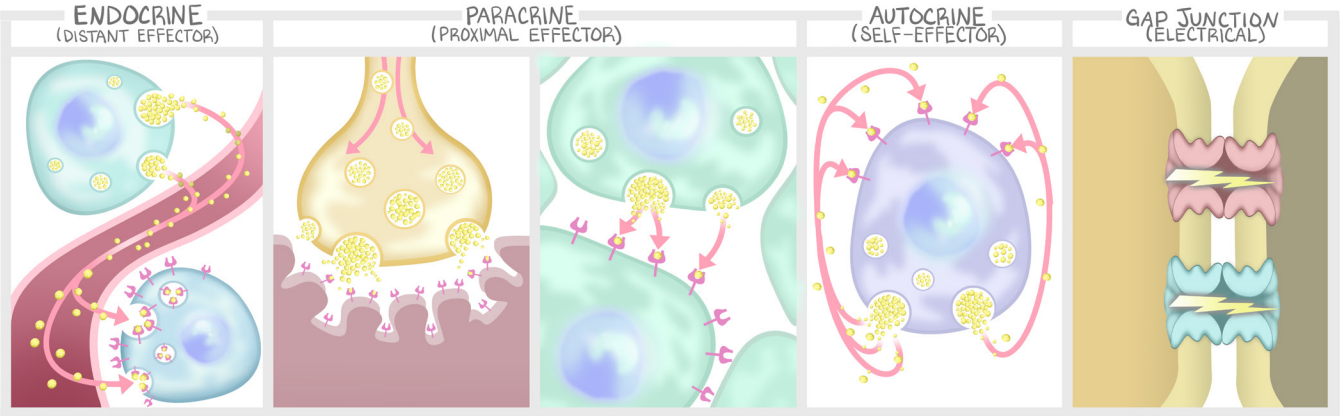

Figure 5.1: Types of Intercellular Communication
Endocrine signals travel a long distance from releasing cell to target; the endocrine system speaks organ to organ through the bloodstream. Paracrine signaling is the release of neurotransmitter very close to the cell meant to feel the effect. The CNS and the neuromuscular junction, all synapses in general, use paracrine signaling. Autocrine is when the cell that releases the signal receives the signal as well. Gap junctions have no ligand and receptor, representing a contiguous cytoplasm.

Chemical Signaling

Chemical signaling occurs between two cells that do not have contiguous cytoplasm. One cell releases a chemical signal, called a **ligand**. Ligands come in various forms, as will be explored below. The ligand will activate a **receptor** on another cell. The relationship of the "releaser" and "message receiver" defines the terminology of chemical signaling. The **effector cell** is the cell that receives the signal, and does something because of the signal.

Endocrine signaling comes from one organ that releases its ligand—**a hormone**—into the bloodstream to affect a target cell distant from the site of release. Chemical signals that are between two different organs must travel through the bloodstream to exert their effects. Therefore, hormones must have long half-lives to travel between the releaser and the receiver. "Endocrine" means "far away chemical signaling through the bloodstream."

Paracrine signaling is when the transmitting cell releases a transmitter very near the effector cell, usually in the same organ or tissue. This is how neurotransmitters at the synaptic cleft communicate. Rapid turnover of these ligands is necessary for regulation.

Autocrine signaling occurs when the hormone secreted produces an effect on the same cell that released the hormone. This is often a feedback mechanism, as when norepinephrine binds α_2 receptors, silencing norepinephrine release.

Extracellular Receptors vs. Intracellular Receptors

Hydrophilic ligands bind to **hydrophilic receptors** on the extracellular matrix side of the cell membrane. That binding of the ligand to the receptor is translated into the cytoplasm somehow. This must be the case for hydrophilic ligands—they have no access through the cell membrane. The "somehow" is what we're going to go over in this lesson.

Lipophilic ligands can freely pass the cell membrane without a channel. This means that lipophilic ligands can get into the cytoplasm or nucleus and act on intracellular receptors. And while a lipophilic ligand could activate a cell membrane receptor, I want you to learn it binary: lipophilic in the cell, hydrophilic on the cell surface.

FEATURE	EXTRACELLULAR	INTRACELLULAR
Ligand	Peptide/protein/catecholamine	Steroid-/lipid-soluble hormones
Binding site	Hormone binds extracellularly	Hormone binds intracellularly
Effector	Intracellular domain transmits effects	Hormone-receptor combo exacts effects
Cascade	Second messenger cascade	No cascade, direct effects
Gene transcription	Gene transcription modification possible (CREB)	Modifies gene transcription (HRE, HREBP)
Method of action	Primary effects made by (de)phosphorylation	Modifies gene transcription (HRE, HREBP)
Speed of change	Changes are fast—minutes and hours	Changes are slow—hours to days

Table 5.1: Comparing Extracellular and Intracellular Receptors

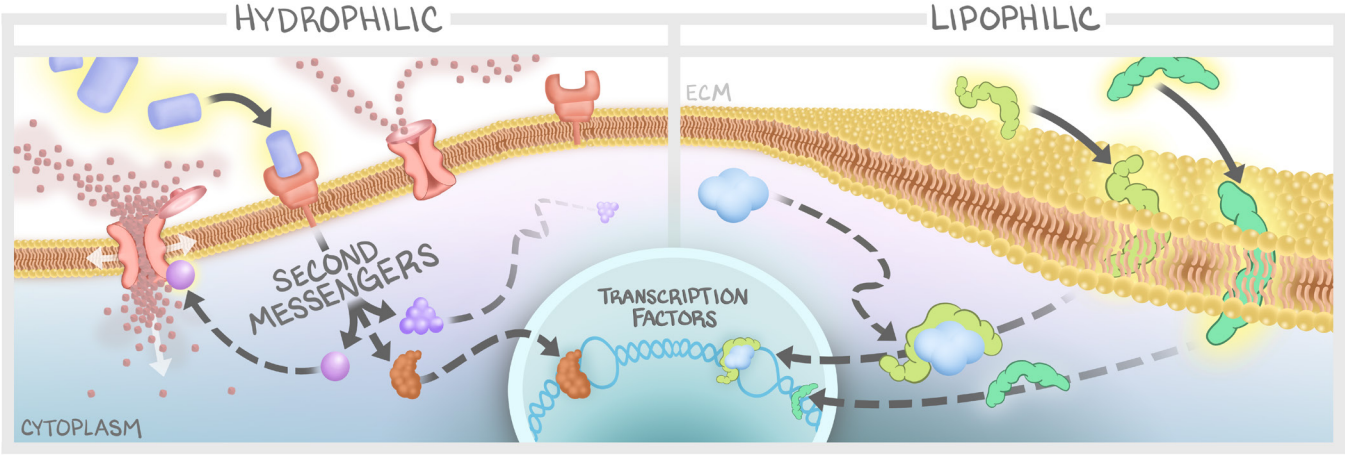

Figure 5.2: Hydrophilic vs. Lipophilic Chemical Signaling
Ligands are either hydrophilic or lipophilic. Hydrophilic means they cannot pass the cell membrane, so must activate transmembrane proteins by binding to the active sites on the extracellular matrix. They then transduce the signal into the cytoplasm where second messengers exert the intended effect. Lipophilic ligands, like steroid hormones, pass through the plasma membrane, find the intracellular (or intranuclear) target, and usually exert their effect via gene transcription regulation.

Receptors That Are Ion Channels (Ionotropic)

Receptors that are gated pores that open in response to binding a ligand are called **ionotropic receptors**. Ionotropic receptors respond to **direct ligands**, so named because the binding of the ligand to its receptor "directly" opens the gate on the pore without any intermediate steps. Examples of ionotropic receptors include the nicotinic acetylcholine receptor of skeletal muscle or the GABA receptor in the brain. The bottom line: binding a ligand opens a channel. The channel is permeable to an ion, allowing that ion to move down its concentration gradient. The movement of the ion changes the membrane potential of that cell. In this case, there are no second messengers.

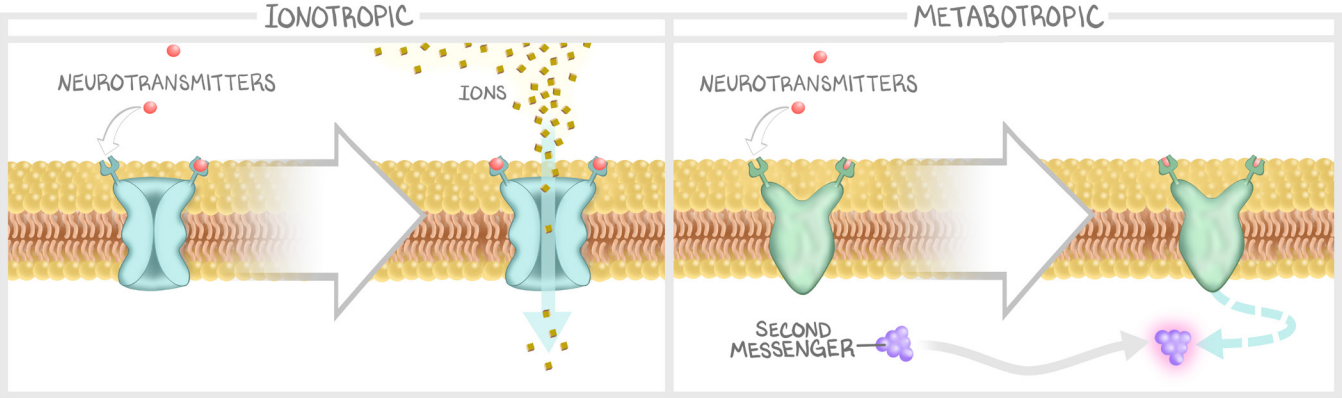

Figure 5.3: Hydrophobic Ligand-Receptor Activation: Ionotropic and Metabotropic
Activation of a receptor bound to its ligand that opens a pore and allows the passage of ions is called ionotropic. Activation of a receptor bound to its ligand that exerts a non-pore-opening effect is called metabotropic.

Receptors That Are Not Ion Channels (Metabotropic)

In contrast to ionotropic receptors, metabotropic receptors act metabolically, meaning the binding of a ligand does something other than open a channel. The how and what of that "something" is the discussion of the rest of this lesson.

Since they do not immediately result in the opening of a pore, the ligands that activate metabotropic receptors are known as indirect ligands. The receptors are transmembrane integral proteins that have no pore but instead communicate to a cytoplasmic second messenger once bound by an extracellular ligand. What happens next can vary, as the mechanisms of intracellular second messengers are vast, and, except when studying specific receptor systems, the downstream effect cannot be anticipated. Generally speaking, the downstream effect could be ion channel activation, (de)phosphorylation of proteins, or alteration of gene expression through inhibition or activation of transcription factors.

Memorizing all the various metabotropic receptors, second messenger systems, and downstream effects is not necessary, but you should learn those we discuss here. We'll go through receptors linked to G proteins, then catalytic receptors (tyrosine kinase), and finish with lipophilic receptors. Lipophilic receptors (steroids) do not open channels, thus are technically metabotropic, and thus would normally activate second messengers—but these rarely do. Instead, they often translocate to the nucleus and act as transcription factors.

Receptors Linked to G Proteins

G proteins are a superfamily of **GTP-binding proteins**. They are **heterotrimers**, consisting of a β subunit, a γ subunit, and an α subunit, bound to GDP at rest. This trimer is an integral protein on the cytoplasmic side of the membrane and does not span the membrane, but it's associated with a **7-transmembrane protein** that does span the membrane. The **extracellular domain** acts as the binding site for ligands. When a ligand binds, a signal is transduced from the extracellular matrix to the cytoplasm, where the **intracellular domain** translates the signal to the G protein trimer.

Before the activation signal arrives, the **trimer** is bound to **GDP** and is **inactive**. The β-γ dimer will never separate. However, when the ligand binds to the extracellular receptor, a conformational change is induced, promoting the exchange of GDP for **GTP on the α subunit**. When bound to GTP, the a subunit dissociates from the trimer **and activates an intracellular target**, initiating an intracellular second messenger system.

The outcomes—potentially infinite—cannot be predicted, as each subunit has a variety of forms. Also, technically, the β-γ dimer also has targets, but these are beyond the scope of this course. Learn that the **α-GTP is the active form** and does the work. When its work is done, the **α subunit hydrolyzes GTP to GDP**, allowing it to reassociate with the β-γ subunits, and returning the trimer to its resting state.

Though the OUTCOME is impossible to predict, the MECHANISM is constant. Let's move on to the two main second messenger systems you need to be familiar with: system 1 and system 2. They are distinguished by the G proteins/receptors involved.

System 1: G_S and G_i

This second messenger system has two receptors from two different G proteins that converge at one common entry point to regulate intracellular messaging. When a ligand binds to the extracellular portion of the **$G_{stimulatory}$ (G_S)** receptor, the intracellular G_S a subunit is activated, which initiates the second messenger pathway within the cell. When a ligand binds to the extracellular portion of the **$G_{inhibitory}$ (G_i)** receptor, the intracellular G_i a subunit is activated, which inhibits the pathway. Both G_S and G_i **target adenylyl cyclase**–G_S activating it, G_i inhibiting it.

Adenylyl cyclase converts ATP into **cAMP** (cyclic AMP). cAMP then increases the activity of **protein kinase A**. Protein kinase A, like all kinases, adds phosphates to things. As discussed above, you don't need to memorize all the variable downstream targets (ion channels, (de)phosphorylation, transcription factors). However, you should learn the special transcription factor mechanism that responds to cAMP—**CREB** (cAMP response element binding protein). When activated, CREB will translocate to the nucleus and bind a **CRE** (cAMP response element). **Elements** are strands of DNA that are the binding site for DNA-binding proteins.

MEMORIZE: *Adenylyl cyclase, cAMP, protein kinase A.*

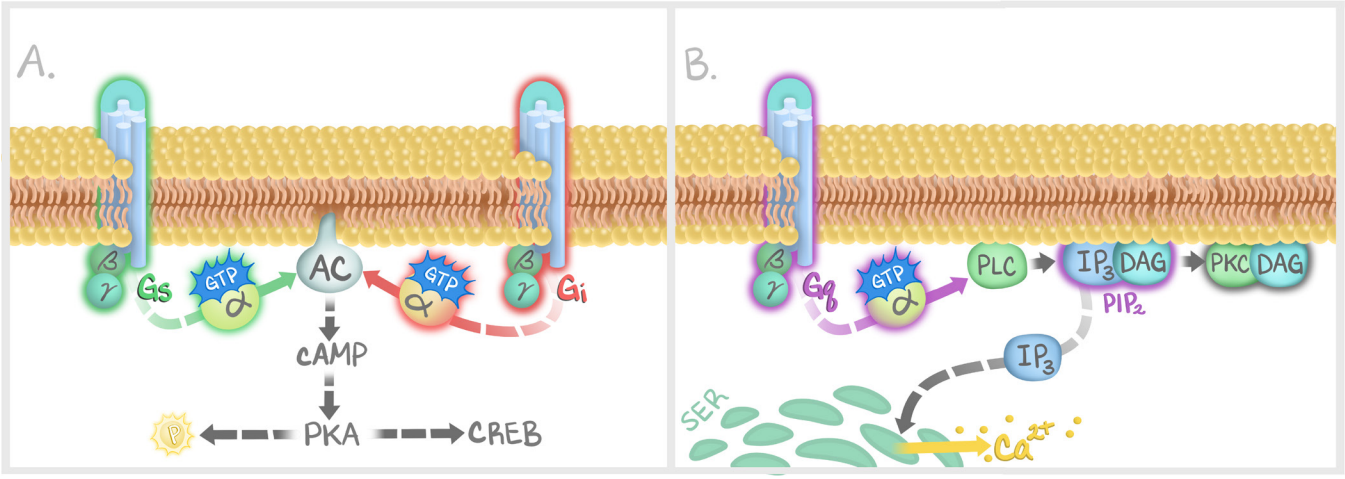

Figure 5.4: G-Protein-Coupled Receptors Specifics
(a) System 1: G_S stimulates adenylyl cyclase (AC), while G_i inhibits it. AC creates cAMP. Rising levels of cAMP stimulate protein kinase A. (b) System 2: G_q involves phospholipase C and cleavage of PIP_2 into cytoplasmic IP_3 (which releases calcium) and membrane-bound DAG (which activates protein kinase C, downregulating the IP_3 pathway).

System 2: G_q

This second messenger system uses G_q (which I remember as "G_{queer}" because it's different than the other two). This receptor activates the α subunit of **G_q**, displacing GDP with GTP, causing the α subunit to dissociate from the trimer and **activating phospholipase C** (PLC). PLC is a phospho-lipase (as in phospholipid bilayer), and is itself embedded in the cell membrane. It cleaves phosphoinositide (PIP_2), releasing **inositol triphosphate** (IP_3) into the cytoplasm, and leaves diacylglycerol (DAG) attached to the cell membrane. IP_3 goes to the sarcoplasmic reticulum and causes **calcium release** into the cytoplasm. How calcium leads to a contraction is discussed in #15: *Smooth Muscle*. Ca^{++} is the action part of this system.

DAG is the off-switch that prevents IP_3 from running amok. DAG activates protein kinase C, which acts as a feedback mechanism to inhibit IP_3, thereby inhibiting calcium influx. G_q-PIP_2-IP_3-Ca is seen almost exclusively in smooth muscles.

MEMORIZE: *Phospholipase C — PIP_2 — IP_3 / DAG — Ca — protein kinase C*

Catalytic Receptors = Tyrosine Kinases

This term, "catalytic receptor," refers to a large category of receptors that have enzymatic activity on the cytoplasmic side. They come in various forms: guanylyl cyclases, serine/threonine kinases, tyrosine phosphatases, tyrosine kinase-associated, and lastly, the one you really need to know, **tyrosine kinase receptors**.

The tyrosine kinase receptor system **JAK/STAT** has been implicated in malignancy (CML) as well as some thrombocytosis disorders. JAK/STAT is also the first truly targeted molecular therapy against malignancy in the form of a tyrosine kinase inhibitor, imatinib. In CML, a **translocation** occurs, creating the **Philadelphia chromosome**, t9;22, the BCR/ABL **oncogene**. Lots of words, all synonyms for each other. In this state, the JAK receptors are overexpressed and overactivated.

When inactive, the JAK receptor exists as a **monomer**. When a ligand binds, two monomers **dimerize** and **autophosphorylate**, creating the active form of the receptor. Strictly speaking, the receptor is now a dimer of two monomers, and each monomer cross-phosphorylates the other, but because the dimer is considered "one receptor" it is said to autophosphorylate. Being phosphorylated activates dimer kinase activity to more than just the dimer; it activates kinase activity associated with cytoplasmic proteins, specifically **STAT**. The phosphorylation of STAT as an intracellular second messenger results ultimately in **cell proliferation** and can, in the diseased translocation, overrule checks in the cell cycle.

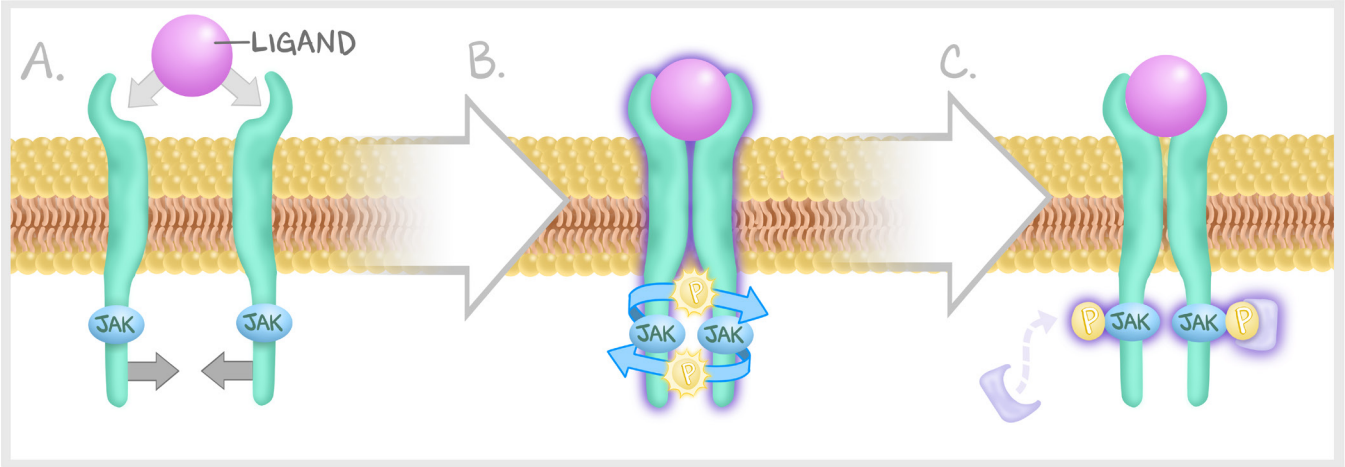

Figure 5.5: Receptor Tyrosine Kinases
Learn this as receptor tyrosine kinase, even though serine . . . and related . . . and whatever. RTK is what you should remember. (a) Monomers exist without activity. Ligands bind, inducing (b) dimerization and autophosphorylation of the dimer (cross-phosphorylation between monomers). Phosphorylation can lead to kinase or phosphatase activity on intracellular second messengers. Remember JAK (receptor), STAT (gets phosphorylated and thereby activated).

Lipophilic Receptors (Cytoplasmic or Nuclear)

Instead of targeting receptors on the cell surface, some ligands can cross the cell membrane and target lipophilic receptors within the cell. Lipophilic receptors are present within the cytoplasm. They have no second messenger system. They do not bind extracellular targets and communicate them into the cytoplasm. They do not open ion channels. Instead, they are often **transcription factors** awaiting activation.

These cytoplasmic receptors exist in an **inactivated state**, inactivated by bound **chaperone** molecules. These chaperone molecules **prevent translocation** of the cytoplasmic receptor to the nucleus. When a lipophilic ligand binds to its lipophilic receptor, the chaperon molecule is removed, unmasking a **nuclear transport signal**, allowing the receptor-ligand combination to migrate to the nucleus and bind DNA.

The regions of DNA that these transcription factors bind to are called HREs (hormone response elements). The receptor itself is often the transcription factor, which in this context can be referred to as a HREB (hormone response element binding protein).

Examples include vitamin D, thyroid hormones, and steroid hormones such as cortisol.

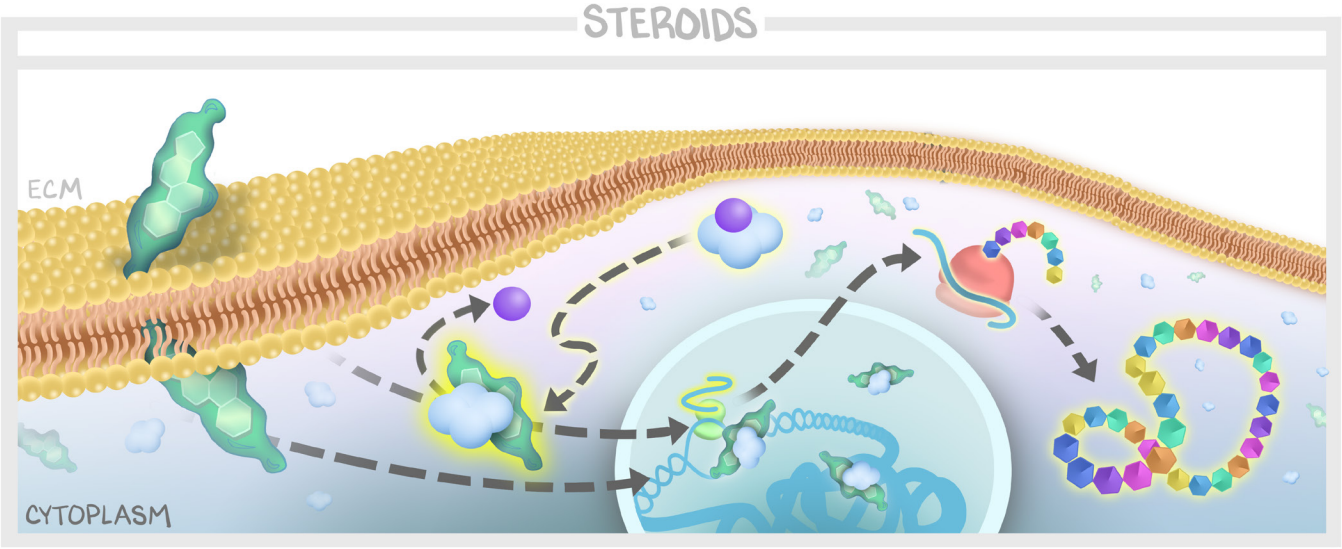

Figure 5.6: Lipophilic Receptors
Lipophilic ligands (almost always steroid hormones) can pass through the plasma membrane and need not interact with extracellular receptors. Often steroid hormone receptors are cytoplasmic if not intranuclear. The binding of a ligand to the receptor releases the receptor from its chaperone, translocates to the nucleus, and exacts its effects through gene transcription.